REMARKS

Applicants respectfully request reconsideration of the present application.

SPECIFICATION

Applicants have amended the specification to correct inadvertent typographical errors.

Applicants respectfully submit that the following three terms are obvious errors, correction of which would be readily apparent to one of ordinary skill in the art:

[flunariziim] **flunarizine**

[varapamyl] **verapamil**

No new matter has been added.

CLAIMS

Claims 1-10 are pending. Claims 11-18 were previously cancelled, without prejudice or disclaimer.

OATH/DECLARATION

The PTO disqualified the reissue oath/declaration as defective. The PTO also disqualified the supplemental reissue oath/declaration for being based on a defective original oath/declaration.

In response, Applicants submit a substitute reissue declaration, which replaces the original reissue declaration submitted February 19, 2004; the first supplemental reissue declaration submitted March 30, 2006 and the second supplemental reissue declaration submitted March 23, 2007. The attached substitute reissue declaration is signed by one inventor, namely Keiji Kubo. The present response is filed simultaneously with a Petition Under 37 C.F.R. § 1.47(a) and 37 C.F.R. § 1.182 to accept the Substitute Reissue Declaration without the signature of Yoshiyuki Inada because he can not be reached.

REJECTION UNDER 35 U.S.C. § 251

Claims 4-10 stand rejected as based upon a defective reissue oath/declaration. Applicants believe that the substitute reissue declaration obviates the rejection.

SPECIFICATION OBJECTION

The PTO objected to the specification because of informalities identified on page 3 of the Office Action. Applicants believe that the amended specification obviates the objection.

CLAIM REJECTIONS UNDER 35 U.S.C. §112, ¶ 1

Claims 1, 2 and 7-10 stand rejected because the specification, while being enabling for the method of treating hypertension, does not provide enablement for the method of treating the broader scope of "angiotensin II-mediated diseases". Applicants respectfully traverse.

The PTO bases the rejection largely on the thesis that "angiotensin II receptor antagonists *may increase the risk of myocardial infarction*", see page 4 of the Office Action, which the PTO supports by the article, Strauss and Hall, Circulation 2006; 144; 838-854.

The safety of a pharmaceutical product is not a condition of patentability

In response, Applicants submit that the safety of a pharmaceutical product is not a condition of patentability of such a product. It is not the role of the PTO to ensure the safety of a pharmaceutical product for humans, but rather of the FDA. "The Patent Office is not the FDA and cannot require evidence that pharmacologically active compounds are safe, effective, and reliable for use with humans." In re Krimmel, 30 USPQ 215 (CCPA 1961).

Strauss et al. ignores results of CHARM study that demonstrates reduction of miocardical infarction by candesartan

Applicants further submit that the thesis, upon which the PTO relies to support its position, is highly controversial and is not widely supported and accepted by those of ordinary skill in the art. For example, the very same article by Strauss and Hall that the PTO uses to support the thesis contains on page 854 "Response to Strauss and Hall", in which Drs.

Tsuyuki and McDonald state "Our basic thesis was simple: ARBs do not increase risk of MI" (ARB is angiotensin II receptor blocker, MI is miocardical infarction). In the last sentence of their "Response to Strauss and Hall", Drs. Tsuyuki and McDonald conclude that "although Drs Strauss and Hall have coined the phrase "the ARB paradox," we are left wondering where the paradox is" referring to the ARB-MI paradox defined on page 839 of Strauss.

Applicants submit that the ARB-MI paradox was introduced in a paper coauthored by Strauss, Verma and Strauss, BMJ, 2004, 329, 1248-1249, based on the data from the VALUE trial, which showed a relative increase in MI for one particular angiotensin II antagonist, valsartan, see Strauss, page 839. In his CIRCULATION paper, which was cited by the PTO, Strauss tries to fit the data from clinical trials for other angiotensin II antagonists into his "paradox" theory. In doing so, Strauss tends to disregard the data that do not support his paradox. For example, Strauss disregards the data from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program in making his conclusions, although he explicitly admits the following results of the CHARM: "Candesartan reduced all-cause mortality (hazard ratio 0.91, 95 % confidence interval [CI] 0.83 to 1.0, P=0.055)" see page 844, left column; "a reanalysis of CHARM suggests candersartan reduces the composite outcome of CV death or non fatal MI", see page 844, left column; "there was a reported nonsignificant reduction in MI (candesartan 57 versus placebo 73; P=0.15), see page 846, right column.

Applicants respectfully submit that to access the effect of the claimed angiotensin II antagonists on myocardial infarction, one or ordinary skill in the art would not have relied on Strauss and his controversial "paradox" theory. Instead, one of ordinary skill in the art would look at the results of the CHARM program in the enclosed paper by Demers et al. JAMA, 2005, 294(14), 1794-1798, which demonstrate that "candesartan significantly reduces the risk of the composite outcome of cardiovascular death or nonfatal MI", see Conclusion, page 1794.

In sum, the PTO's rejection relies on a controversial theory, which ignores real experimental results demonstrating the reduction of the risk of MI by the claimed angiotensin II antagonists. For this reason alone, Applicants request withdrawal of the rejection.

The PTO's position is inconsistent with allowance of U.S. Patent No. 6, 107,323

On an additional note, Applicants submit that the ground for rejection here is wholly inconsistent with PTO's examining and allowing method claims reciting "angiontensin-II mediated disease" *in the very patent on which Applicants now seek reissue*. In this regard, the PTO examined and allowed similar method claims reciting "angiotensin-II mediated disease" in commonly assigned U.S. Pat. No. 6,107,323 (*see* claims 1 and 7; copy provided in Appendix A).

For all these reasons, Applicants request the PTO to reconsider and withdraw this ground for rejection.

CLAIM REJECTIONS UNDER 35 U.S.C. §103

Claims 1-10 stand rejected as obvious over Naka (EP 0520423 and EP 0459136) in view of Weinstock (WO/10097) further in view of Wong (caplus AN 91307690, American Journal of Hypertension, vol. 4, 288S-298S, 1991). Applicants respectfully traverse.

The PTO's formulation of the rejection

The PTO formulates the rejection on pages 7-8 of the Office Action as follows:

1) Naka et al. teaches the claimed angiotensin II receptor antagonist useful for treatment hypertension citing: EP 0459136 for teaching (±)-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate and 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7- carboxylic acid, and EP 0520423 for teaching 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methy l]-1H-benzimidazole-7-carboxylic acid.

2) The PTO admits that the difference between the instant claims and the prior is the requisite presence of an additional ingredient (i.e. furosemide or a calcium antagonist).

3) The PTO states that Weinstock teaches the combination of angiotensin II antagonists with diuretics (e.g. amiloride, metolazone, spironolactone) or calcium antagonists for the treatment of hypertension.

4) The PTO asserts that Wong specifically teaches the combination of furosemide and Dup 753 (an angiotensin II receptor antagonist)

5) Then the PTO asserts that "one of ordinary skill would be motivated, from the disclosure in the prior art, to make the modification required to have arrived at the instant invention: i.e., to combine the claimed compound with diuretics and/or calcium antagonists for the purpose of treating hypertension."

6) Furthermore, it is obvious according to the rejection to combine compositions taught by the prior art useful for the same purpose to form a third composition that is to be used for the very same purpose. *In re Kerkhoven*, 205 USPQ 1069 (C.C.P.A. 1980).

Applicants' interpretation of the cited prior art references

In response, Applicants note that while Naka '423 and '136 may teach the claimed antiotensin II antagonists, these documents do not teach the combination and uses of those compounds with a diuretic and/or a calcium channel blocker.

Weinstock teaches pharmaceutical compositions comprising an angiotensin II receptor antagonist and a second agent selected from a diuretic, a calcium channel blocker, a β-adrenoceptor, a renin-inhibitor or an angiotensin converting enzyme inhibitor and a method of treating hypertension with such compositions (see abstract). Specific angiotensin II blocking agents of formula (I)-(IX) disclosed by Weinstock on pages 3-18, do not include the particular angiotensin II antagonists recited in the pending claims 1-10. Applicants submit that Weinstock does not teach that the second agent of his composition, such as a diuretic or a calcium channel blocker, can be used per se, i.e., without Weinstock's angiotensin II antagonist, for treatment of the hypertension. Applicants further submit that the only working example related to antihypertensive activity in Weinstock relates to a combination of a single angiotensin II receptor antagonist, (E)-3-[2-n-butyl-1{(4-carboxyphenyl)methyl}-1H-

imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, and a single diuretic, hydrochlorothiazide (HCTZ), see pages 22-23.

Wong teaches that DuP 753 lowered blood pressure in furosemide pretreated normotensive rats, but not in untreated normotensive rats, see abstract, left column and pages 291S-292S. Applicants submit that one of ordinary skill in the art would not have interpreted Wong's disclosure as teaching a combination of an angiotensin II antagonist and furosemide as asserted by the PTO at least for the following two reasons: 1) furosemide and DuP 753 are not administered as a combination because normotensive rats are first pretreated with furocemide and then treated with DuP 753; 2) the combined effect of furocemide and DuP 753, which is lowering blood pressure in normotensive rats, does not suggest a practical utility in a method such as that presently claimed.

The PTO failed to establish a prima facie case of obviousness

Applicants submit that the PTO failed to establish any prima facie case of obviousness because the PTO failed to make an explicit analysis supporting the combination used in the rejection.

In *KSR International Co. v. Teleflex Inc.*, 550 U.S._, 82 USPQ2d 1385 (2007), the Supreme Court emphasized that the analysis supporting a rejection under 35 U.S.C. §103(a) should be made explicit. The Supreme Court also stated, quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning the legal conclusion of obviousness.'"

Applicants respectfully submit that both statements 5 and 6 in the PTO's formulation of the rejection are conclusory.

With respect to the statement 6, Applicants note that, in *In Kerkhoven* and its related cases, not only were the two compositions known for the same purpose, but they also worked by the very same mechanism. Applicants respectfully urge that this is not the case with the presently claimed invention.

Applicants further note that none of the cited references teaches that a diuretic or a calcium channel blocker *per se*, without an angiotensin II antagonist, can be useful for treatment of hypertension. Thus, even if, for argument's sake, the PTO's interpretation of *In Kerkhoven* were correct, one of ordinary skill in the art would not have combined particular angiotensin II antagonists disclosed Naka with a diuretic and/or a calcium channel blocker to arrive at the claimed invention based on the cited refeences.

As for the statement 5, Applicants believe that the only reasonable interpretation of this statement is that the PTO intended to state that one of ordinary skill in the art would have been motivated to substitute in Weinstock's compositions, Weinstock's angiotensin II antagonist with Naka's angiotension II antagonists. Applicants submit that, to make a rejection proper using such a substitution, the PTO is required to provide "some articulated reasoning with some rational underpinning". As no such reasoning has been provided, Applicants submit that the PTO failed to establish a *prima facie* case of obviousness.

The claimed subject matter demonstrates unexpected results

Applicants submit that, even if for the argument's sake, the PTO had provided the articulated reasoning with a valid rational underpinning supporting the substitution of Weinstock's angiotensin II antagonist with Naka's angiotension II antagonists, the present claims would have still have been unobvious over the cited references because of the unexpected effects of the claimed subject matter, which is evidenced by the enclosed article by Kim *et al.*, *Hypertension*, vol. 35 (2000) 769-774, which Applicants submitted previously with their response filed May 31, 2005, and by Demers et al. *supra*.

In particular, Kim describes that monotherapy of 0.2mg/kg candesartan cilexetil of 0.5 mg/kg amlodipine, which is a known calcium channel blocker, failed to reduce the cardiac mRNAs of the SHRSP (data not shown). However, Kim further disclosed that the *combination* of these drugs significantly decreased left ventricular mRNA levels for ANF, skeletal α-actin, and collagen types I and II, see the paragraph bridging pages 771 and 772.

In CHARM program reported by Demers et al., candesartan significantly reduced the risk of the composite outcome of cardiovascular death or nonfatal MI, see Conclusion, page

1794. As 83% of CHARM program participants were receiving a diuretic in addition to candesartan, see Design, Setting, and Participants, page 1994, the results of the CHARM program demonstrate that a combination of diuretic and candesartan reduces the risk of the composite outcome of cardiovascular death or nonfatal MI.

The PTO has allowed composition claims identical in scope to claims 1-3

Notwithstanding all the above considerations, Applicants respectfully note, with respect to claims 1-3, that the PTO allowed composition claims of identical scope in the parent application, now U.S. Pat. No. 6,228,874. Because the PTO granted these claims, Applicants respectfully submit that no reason exists why the present method claims should not also be allowable.

Conclusion

For all of these reasons, the claims are patentable over Naka, Weinstock and Wong. Accordingly, Applicants respectfully request the PTO to reconsider and withdraw the rejection.

DOUBLE PATENTING REJECTIONS

The PTO has issued six non-statutory obvious type double patenting rejections, five of which are multiple-reference double-patenting rejections citing one of U.S. patents nos. 5,736,555; 5,583,141; 5,243,054; 7,294,344 and 6,589,547, as a primary reference, in combination with Weinstock et al. (WO 92/10097) further in view of Wong et al. (caplus AN 91307690, American Journal of Hypertension, vol. 4, 288S-298S, 1991). Prior to addressing each of the obviousness-type rejections individually, Applicants provide the following commentary related to the five multiple reference obviousness type rejections. The PTO formulates each of the five multiple reference double patenting rejections following the pattern used in the obviousness rejection over Naka, Weinstock and Wong. Applicants submit that none of the claims of U.S. patents nos. 5,736,555; 5,583,141; 5,243,054; 7,294,344 and 6,589,547 recites the angiotensin II antagonists in combination with a diuretic and/or a calcium channel blocker. The deficiencies of the multiple-reference obviousness

type rejections are the same deficiencies set forth above in the PTO's obviousness rejection. 1) The PTO fails to present a *prima facie* case of obviousness because it uses conclusory statements and fails to make the explicit analysis supporting the combination used in the rejection; 2) the PTO misinterprets Weinstock, which, in fact, does not teach the use of a calcium channel blocker or a diuretic *per se*, without an angiotensin II antagonist, for treatment of hypertension; 3) the PTO misinterprets Wong, which, contrary to the PTO's assertion, does not teach a combination of an angiotensin II antagonist and a furosemide; 4) the PTO incorrectly applies *Kerkhoven* type logic to a situation where different mechanisms are involved. In addition, the unexpected effects of the claimed subject matter evidenced by Kim et al. support patentability of the instant claims over the claims of each of U.S. Patent Nos. 5,736,555; 5,583,141; 5,243,054; 7,294,344 and 6,589,547 taken in combination with Weinstock and Wong.

Claims 1-10 stand rejected on the ground of non-statutory obviousness-type double patenting as unpatentable over claims 1-6, 8-12, 14-16, 19, 20 and 23-25 of U.S. Patent No. 5,736,555 in view of Weinstock et al. (WO 92/10097) further in view of Wong et al. (caplus AN 91307690, American Journal of Hypertension, vol. 4, 288S-298S, 1991). Applicants respectfully traverse.

As admitted by the PTO on page 10 of the Office Action, the claims of the '555 patent do not recite the particular angiotensin II antagonists of the instant claims. Furthermore, as admitted by the PTO on page 10 of the Office Action, the claims the '555 patent do not recite a combination of angiotensin II antagonist with a calcium channel blocker and/or a diuretic.

Applicants explained above the deficiencies of the PTO's position with respect to the combination of the particular angiotensin II antagonist with a calcium channel blocker and/or a diuretic. Applicants also submit that the unexpected effects of the claimed subject matter evidenced by Kim et al. and Demers et al. support patentability of the instant claims over the claims of the '555 patent taken alone or in combination with Weinstock and Wong.

In sum, at least for these reasons, the claims are patentable over the '555 patent, Weinstock and Wong. Accordingly, Applicants respectfully request the PTO to reconsider and withdraw the rejection.

Claims 1-10 stand rejected on the ground of non-statutory obviousness-type double patenting as unpatentable over claims 1-6, 8-16, 19, 20 and 23-25 of U.S. Patent no. 5,583,141 in view of Weinstock et al. (WO 92/10097) further in view of Wong et al. (caplus AN 91307690, American Journal of Hypertension, vol. 4, 288S-298S, 1991). Applicants respectfully traverse.

As admitted by the PTO on page 11 of the Office Action, the claims of the '141 patent do not recite the particular angiotensin II antagonists of the instant claims. Furthermore, as admitted by the PTO on page 11 of the Office Action, the claims the '141 patent do not recite a combination of angiotensin II antagonist with a calcium channel blocker and/or a diuretic.

Applicants explained above, the deficiencies of the PTO's position with respect to the combination of the particular angiotensin II antagonist with a calcium channel blocker and/or a diuretic prevent the establishment of any case of *prima facie* obviousness. Applicants also submit that the unexpected effects of the claimed subject matter evidenced by Kim et al. and Demers et al. support patentability of the instant claims over the claims of the '141 patent taken alone or in combination with Weinstock and Wong.

In sum, at least for these reasons, the present claims are patentable over the '141 patent, Weinstock and Wong. Accordingly, Applicants respectfully request the PTO to reconsider and withdraw the rejection.

Claims 1-10 stand rejected on the ground of non-statutory obviousness-type double patenting as unpatentable over claim 1 of U.S. Patent no. 5,243,054 in view of Weinstock et al. (WO 92/10097) further in view of Wong et al. (caplus AN 91307690, American Journal of Hypertension, vol. 4, 288S-298S, 1991). Applicants respectfully traverse.

As admitted by the PTO on page 12 of the Office Action, the claims the '054 patent do not recite a combination of angiotensin II antagonist with a calcium channel blocker and/or a diuretic.

Applicants explained above the deficiencies of the PTO's position with respect to the combination of the particular angiotensin II antagonist with a calcium channel blocker and/or a diuretic, which prevent the establishment of any case of *prima facie* obviousness. Applicants also submit that the unexpected effects of the claimed subject matter evidenced by Kim et al. and Demers et al. support patentability of the instant claims over the claims of the '054 patent taken alone or in combination with Weinstock and Wong.

In sum, at least for these reasons, the claims are patentable over the '054 patent, Weinstock and Wong. Accordingly, Applicants respectfully request the PTO to reconsider and withdraw the rejection.

Claims 1-10 stand rejected on the ground of non-statutory obviousness-type double patenting as unpatentable over claims 1-15 and 17 of U.S. Patent no. 7,294,344 in view of Weinstock et al. (WO 92/10097) further in view of Wong et al. (caplus AN 91307690, American Journal of Hypertension, vol. 4, 288S-298S, 1991). Applicants respectfully traverse.

As admitted by the PTO on page 14 of the Office Action, the claims the '344 patent do not recite a combination of angiotensin II antagonist with a calcium channel blocker and/or a diuretic.

Applicants explained above the deficiencies of the PTO's position with respect to the combination of the particular angiotensin II antagonist with a calcium channel blocker and/or a diuretic, which prevent the establishment of any *prima facie* case of obviousness. Applicants also submit that the unexpected effects of the claimed subject matter evidenced by Kim et al. and Demers et al. support patentability of the instant claims over the claims of the '344 patent taken alone or in combination with Weinstock and Wong.

In sum, at least for these reasons, the claims are patentable over the '344 patent, Weinstock and Wong. Accordingly, Applicants respectfully request the PTO to reconsider and withdraw the rejection.

Claims 1-10 stand rejected on the ground of non-statutory obviousness-type double patenting as unpatentable over claims 1-15 and 17 of U.S. Patent no. 6,589,547 in view of Weinstock et al. (WO 92/10097) further in view of Wong et al. (caplus AN 91307690, American Journal of Hypertension, vol. 4, 288S-298S, 1991). Applicants respectfully traverse.

As admitted by the PTO on page 15 of the Office Action, the claims the '547 patent do not recite a combination of angiotensin II antagonist with a calcium channel blocker and/or a diuretic.

Applicants explained above the deficiencies of the PTO's position with respect to the combination of the particular angiotensin II antagonist with a calcium channel blocker and/or a diuretic, which prevent the establishment of any *prima facie* case of obviousness. Applicants also submit that the unexpected effects of the claimed subject matter evidenced by Kim et al. and Demers et al. support patentability of the instant claims over the claims of the '547 patent taken alone or in combination with Weinstock and Wong.

In sum, at least for these reasons, the claims are patentable over the '547 patent, Weinstock and Wong. Accordingly, Applicants respectfully request the PTO to reconsider and withdraw the rejection.

Claims 4-10 stand rejected on the ground of non-statutory obviousness-type double patenting as unpatentable over claims 1-4 of U.S. Patent no. 6,420,405. Applicants respectfully traverse.

Applicants believe that the terminal disclaimer over U.S. Patent no. 6,420,405 submitted with the present response obviates the rejection.

CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Sept. 9, 2008

By _____

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